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EXAMINER

KERR, KATHLEEN M

ART UNIT

PAPER NUMBER

1652

DATE MAILED: 10/15/2003

28

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/478,598

Applicant(s)

RAO ET AL.

Examiner

Kathleen M Kerr

Art Unit

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 14 August 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 54-58,60-65,67-72,75-80,82,97-105 and 119-125 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 54-58,60-65,67-72,75-80,82,97-105 and 119-125 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____
- 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other:

DETAILED ACTION

Application Status

1. In response to the previous Office action, a non-Final rejection (Paper No. 25, mailed on April 28, 2003), Applicants filed a response and amendment received on July 25, 2003 (Paper No. 26). Said amendment cancelled Claim 83, amended Claims 54, 57, 58, 64, 65, 67-69, 72, 79, 80, 82, 97-99, 104, 105, and 124, and added new Claim 125. Thus, Claims 54-58, 60-65, 67-72, 75-80, 82, 97-105, and 119-125 are pending in the instant Office action and will be examined herein.

The Examiner notes that in the presentation of the claims, Applicants note that Claim 123 is "currently amended"; however, no amendment is found. It would seem that an amendment like Claim 104 is appropriate. Also noted is that Claim 80 is amended, although it is incorrectly cited as "previously presented".

Priority

2. As previously noted, the instant application is granted the benefit of priority for the U.S. non-Provisional Application No. 08/988,015 filed on December 10, 1997.

Drawings

3. As previously noted, the drawings have been approved by the Draftsmen and are, therefore, entered as formal drawings acceptable for publication upon the identification of allowable subject matter.

Information Disclosure Statement

4. The information disclosure statement filed August 14, 2003 has not been considered because the appropriate fee did not accompany the request. This fee (or certification) is required after a first Office action on the merits (see 37 C.F.R. § 1.97).

Withdrawn - Claim Rejections - 35 U.S.C. § 112, second paragraph

5. Previous rejection of Claims 54-58, 60-65, 67-72, 75-80, 82, 83, 97-105, and 119-124 under 35 U.S.C. § 112, second paragraph, as being indefinite is withdrawn by virtue of Applicants' amendment.

6. Previous rejection of Claims 64 and 79 under 35 U.S.C. § 112, second paragraph, as being indefinite is withdrawn by virtue of Applicants' amendment.

7. Previous rejection of Claims 64, 79, and 104 under 35 U.S.C. § 112, second paragraph, is withdrawn by virtue of Applicants' amendment. The amendment of Claim 123 to correct this confusion seems to have been inadvertently omitted (see maintenance of rejection below).

8. Previous rejection of Claim 67 under 35 U.S.C. § 112, second paragraph, as being indefinite for antecedent basis is withdrawn by virtue of Applicants' amendment.

9. Previous rejection of Claim 99 under 35 U.S.C. § 112, second paragraph, as being indefinite for the phrase "rather than" is withdrawn by virtue of Applicants' amendment.

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Maintained - Claim Rejections - 35 U.S.C. § 112, second paragraph

10. Previous rejection of Claim 123 under 35 U.S.C. § 112, second paragraph, as being indefinite is maintained. An amendment of Claim 123 (as in Claims 64, 79, and 104) to correct this confusion seems to have been inadvertently omitted.

Withdrawn - Claim Rejections - 35 U.S.C. § 112, first paragraph

11. Previous rejection of Claim 99 under 35 U.S.C. § 112, first paragraph, new matter, is withdrawn by virtue of Applicants' amendment.

New or Maintained - Claim Rejections - 35 U.S.C. § 112, first paragraph

The Examiner has divided the previous, single enablement rejection into several rejections to focus on all the issues previously presented. All pending claims are rejected under enabled to some extent.

12. Previous rejection of Claims 54-57, 67, 68 (new), 82, 119-124, and 125(new) under 35 U.S.C. § 112, first paragraph, enablement due to the requirement of alteration of at least 10% of the amino acid content of the protein, is maintained (or added for Claims 68 and 125).

Applicants' arguments have been fully considered but are not deemed persuasive for the following reasons. Applicants do not present any arguments specific for why disclosure of an effective method altering 8.25% of the amino acid content while maintaining native conformation enables a method altering at least 10% of the amino acid content, even though this issue was specifically presented previously by the Examiner:

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“ ‘At least 10%’ alteration of amino acid content

The instant specification provides no working examples for producing a mutant VSP protein that maintains native conformation while having been altered in its amino acid composition by at least 10%. The example in the specification changes the content by 8.25%. Description of more extensive mutants is found (see Tables), but none are brought to fruition. It is wholly unpredictable whether or not the native conformation (or even a conformation recognized by the monoclonal antibody described) can be maintained with such extensive modification to the small protein sequence. On page 16 of the specification, it is noted that 51 out of 218 amino acid positions are postulated for mutation to hydrophobic residues and its “possible” that the VSP protein “might tolerate” all of said changes. The state of the prior art is extensive with numerous examples of alteration of amino acid content, but none to the extent of 10% of the amino acid composition while maintaining the native conformation.

Additionally, some of the instant claims are drawn to mutating your own “protein of interest”. No direction as to the allowed changes for every known protein in the art is taught. No working examples, other than that of VSP β , are taught. No antibodies or other protein-of-interest:interacting molecule pairs are taught. In the state of the art, it is highly foreseeable that many proteins cannot be subjected to this level of mutagenesis and maintain any sort of native conformation. The specification presents no guidance for discerning which proteins are suitable for the claimed methods or for discerning where in those suitable proteins mutagenesis would be most productive in the claimed methods.”

13. Previous rejection of Claims 54-57, 69-72, 75-80, 82, and 120-124 under 35 U.S.C. § 112, first paragraph, enablement due to the requirement of using interacting molecules, even specifically antibodies, with *any* protein of interest, is maintained. Applicants’ arguments have been fully considered but are not deemed persuasive for the following reasons. Applicants argue that a set of interacting molecules (antibodies included) can be used to determine an altered protein’s conformation with respect to the native protein conformation. Applicants do not present any arguments specific for why methods of altering and then testing the conformation of *any* protein of interest are enabled by the specification.

All the examples in the specification rely on the set of antibodies specific for VSP or rely on VSP homo- and heterodimers. No enabling description of the use of proteins, other than VSP, is found in the specification. The use of panels of antibodies to probe conformation of other proteins is wholly unpredictable and without working example or guidance in the specification. Is the number of antibodies a function of the length of the protein (21 antibodies are sufficient for a 218 amino acid protein so 42 antibodies would be sufficient for a 436 amino acid protein)? How can the complexity (folds, sheets, helices) of the protein molecule be accounted for if it is only a matter of length? Moreover, the use of homodimers for any protein of interest is wholly unfounded since many proteins do not dimerize, or even heterodimerize.

14. Previous rejection of Claims 54, 57, 58, 60-64, 68, 69, 72, 75-80, 82, and 120-124 under 35 U.S.C. § 112, first paragraph, enablement due to the requirement of using *any* interacting molecules is maintained. Applicants' arguments have been fully considered but are not deemed persuasive for the following reasons. Applicants argue that a set of interacting molecules (antibodies included) can be used to determine an altered protein's conformation with respect to the native protein conformation.

As previously noted, interacting molecules encompass not only similar proteins but also nucleotide sequences, carbohydrates, inhibitors and substrates (see page 5 of the specification). No support for the use of such interacting molecules to test for conformation is described in the specification or in the art, to the extent of the genus claimed. The ability to find combinations of proteins of interest and interacting molecules to test protein conformation is wholly unpredictable wherein examples are not already documented in the art.

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15. Previous rejection of Claims 54-58, 60-65, 67-72, 75-80, 82, 97-105, and 119-125 under 35 U.S.C. § 112, first paragraph, enablement due to the requirement of using a set of antibodies to determine VSP protein conformation, is maintained. Applicants' arguments have been fully considered but are not deemed persuasive for the following reasons. Applicants argue that a set of antibodies can be used to determine an altered VSP protein conformation with respect to the native protein conformation. Applicants cite the specification and the declaration under 37 C.F.R. § 1.132, but these citations are not persuasive.

The Examiner agrees that a set of antibodies, if large enough, would be able to identify VSP proteins "**substantially retaining native conformation**"(emphasis in original, see Declaration under 37 C.F.R. § 1.132). The Examiner maintains, however, that interacting molecules cannot determine the conformation (not a substantially similar conformation) of the altered protein. The Examiner suggests amendment of the claim language so that, while the conformation of the altered protein is considered, it need not be determined.

NEW OBJECTIONS/REJECTIONS

Claim Objections

16. Claim 57 is objected to for having improper form. Two periods are at the end of the claim; only one period is appropriate. Correction is required.

Claim Rejections - 35 U.S.C. § 112

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

17. Claims 57, 58, 60-65, 67, 72, and 119 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. It is unclear how a “set of interacting molecules” can form a homodimer. Homodimers, loosely interpreted, are related to using a native protein of interest that naturally forms a homodimer, mutating the protein and interacting it with the wild-type protein form to test for homodimerization. The term “set” of interacting molecules requires that more than one kind of molecule be present in the “set”, particularly in view of Applicants’ arguments concerning enablement of the pending claims. Clarification of Claim 57 is required.

18. Claim 65 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Both filter lift assays and ELISAs (enzyme-linked immunosorbent assay) require antibody interactions. Claim 58, from which Claim 65 depends, excludes antibody interaction for the identification of conformation. Thus, it is unclear how these antibodies-based assays can be utilized. Clarification is required.

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The following is a quotation of the first paragraph of 35 U.S.C. § 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

19. Claims 54, 57, 58, 60-65, 67, 69, 72, 75-80, 82, and 119-124 are rejected under 35 U.S.C. § 112, first paragraph, new matter, as failing to comply with the written description requirement.

The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The instant claims are drawn to methods for altering amino acid composition using “a set of interacting molecules”.

The originally filed specification supports methods using a single interacting molecule and sets of antibodies (see pages 2, 5, 6, 13, and original claims). On page 5, “binding partners and/or interacting molecules” (emphasis added) are described; however, they are not described as being used as a set, together, in a single method. Also on page 5, interacting molecules that are homo- or heterodimers are described as VSP α -VSP α , VSP α -VSP β , and VSP β -VSP β ; these are not considered disclosures of sets of molecules but single, interacting molecules. On page 6, using a set of antibodies is implied in “proteins which exhibit the correct conformation ... can be selected for by the ability to bind antibodies recognizing conformational domains of the native protein”(emphasis added). On page 13, a panel of 21 monoclonal antibodies is used. In original claims 1, 8, and 17, methods using a set of antibodies are supported. Thus, using a set of antibodies is supported, but the more generic claims to using a set of interacting molecules is not. Applicants must delete the new matter or cite clear support in the specification as originally filed to support the genus claimed.

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Summary of Pending Issues

20. The following is a summary of the issues pending in the instant application that **MUST** be addressed in response to the instant Office action:

- a) The IDS filed August 14, 2003 has not been considered for lack of fee payment.
- b) Claim 57 stands objected to for having improper form.
- c) Claim 123 stands rejected under 35 U.S.C. § 112, second paragraph, as being indefinite.
- d) Claims 57, 58, 60-65, 67, 72, and 119 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for how a "set of interacting molecules" can form a homodimer.
- e) Claim 65 stands rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for requiring filter lift assays and ELISAs when antibody use is outside the claim scope.
- f) Claims 54-58, 60-65, 67-72, 75-80, 82, 97-105, and 119-125 stand rejected under 35 U.S.C. § 112, first paragraph, enablement.
- g) Claims 54, 57, 58, 60-65, 67, 69, 72, 75-80, 82, and 119-124 stand rejected under 35 U.S.C. § 112, first paragraph, new matter.

Conclusion

21. No claims are allowed for the reasons identified in the numbered sections of this Office action. Applicants must respond to the objections/rejections in each of the numbered sections in this Office action to be fully responsive in prosecution. The instant Office action is **NON-FINAL** based on new grounds of rejection presented herein.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kathleen M Kerr whose telephone number is (703) 305-1229. The examiner can normally be reached on Monday through Friday, from 8:30am to 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathupura Achutamurthy can be reached on (703) 308-3804. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

KMK

October 14, 2003

